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Prevention of Indwelling Central Venous Catheter Sepsis

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In an attempt to decrease the incidence of central venous catheter sepsis in children with cancer, we conducted a study to evaluate the benefit of adding broad-spectrum antibiotics to the catheter "flush solution." In a prospective, placebo-controlled, double-blinded, randomized trial, 69 children with different types of malignancies were studied. The central venous catheters in these children were flushed with either the standard solution (normal saline + 100 U/ml of heparin) or the study solution (25 μg/ml of both amikacin and vancomycin added to the standard solution). At the conclusion of the study, 64 children with a total of 67 indwelling central venous lines were assessable. The total catheter days on study were 20,700 days, with a median of 323 catheter days per patient. We documented 10 events of catheter-related infections (0.49 events/1,000 catheter days at risk). Five of these events were catheter-related sepsis (0.24 sepses/1,000 catheter days): two were fungal and three were bacterial. Due to the low incidence of catheter-related sepsis in this study, no statement regarding the prophylactic use of antibiotics could be made. The extremely low rate of catheter-related sepsis reported herein may be retrospectively attributed to continuous staff education regarding aseptic techniques in handling these catheters. Staff education is essential, and probably the most effective factor in preventing catheter-related sepsis.

Key words: indwelling central venous catheter, pediatric oncology, sepsis

INTRODUCTION

The indwelling central venous catheter (ICVC) has become an indispensable tool for the care of oncology patients [1]. The long-term venous access that ICVC provides facilitates both blood sampling and the administration of chemotherapy, nutrition, and blood products. The most common complication associated with ICVC in the immunocompromised host is infection [2]. Catheter-related infections can be divided into two main categories: local soft tissue infections at the insertion or reservoir site, and systemic catheter-related septicemias. The latter is more common and associated with significant morbidity and occasional mortality in neutropenic patients [3].

Strategies for prevention of infections are of particular importance in the use of these devices. Schwartz et al. showed that the use of a vancomycin-containing flush solution in immunocompromised patients with central venous catheters can decrease the frequency of catheter-related sepsis associated with vancomycin-susceptible bacteria [4]. Although coagulase-negative staphylococci and *Staphylococcus aureus* are the two most common isolates in catheter-related septicemias, hospital acquired gram-negative bacilli and enteric organisms cause a significant number of catheter-related sepses [1]. To significantly decrease the rate of catheter-related sepsis, we evaluated the prophylactic use of the vancomycin-amikacin combination in the catheter flush solution.

MATERIALS AND METHODS

Study Population

Any patient less than 22 years of age with a diagnosis of malignancy who had an indwelling central venous catheter at the University of Miami/Jackson Memorial Medical Center was eligible for entry onto this prospective study. Patients were eligible for study if an ICVC was previously in place or if one was planned to be placed after patient enrollment. The study protocol was approved by the Institutional Review Board Committee, and an informed written consent form was obtained from the patients and/or their parents/legal guardian.

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TABLE I. Patient Diagnosis on Enrollment

Acute lymphocytic leukemia	33
Acute myelocytic leukemia	1
Brain tumor	4
Hodgkin's lymphoma	3
Non-Hodgkin's lymphoma	3
Neuroblastoma	3
Wilms' tumor	4
Rhabdomyosarcoma	2
Osteogenic sarcoma	3
Ewing's sarcoma	2
Retinoblastoma	2
Germ cell tumor	1
Carcinomas	2
Langerhans cell histiocytosis	1

Study Design

The patients with preexisting ICVC were eligible for randomization only if there was no history of catheter-related sepsis prior to study entry. All patients enrolled on study with catheters placed following enrollment were eligible for randomization. Patients who had a history of catheter-related sepsis prior to study entry were included in the study but were not eligible for randomization. Through a computer-generated random order, patients were assigned to either solution A or solution B. In a blinded fashion the solutions, which had indistinguishable physical appearances, were labeled A or B. The contents of the study solutions were unblinded only at the conclusion of the study, which lasted 17 months. Solution A was the standard solution (normal saline + heparin 100 U/ml), and solution B was the study solution (normal saline + heparin 100 U/ml + vancomycin 25 μg/ml + amikacin 25 μg/ml). The patients not eligible for randomization received the study solution, which labeled as solution C. Patients who were randomized to receive either solution A or B, and who developed a catheter-related sepsis during the study period, were monitored on the study but were crossed over to solution C.

The solutions were used for flushing of the catheters whenever they were utilized. When an enrolled patient received a new catheter, efforts was made to flush the catheter with the appropriate study solution immediately post placement in the operating room. Each flush volume was 5 mls, and all prepared solution vials expired within 4 weeks from preparation.

House staff and nursing staff were asked to use only the assigned flush solution A, B, or C during the study period. Families were given the assigned solution to use in case of emergency access of the ICVC outside the medical center. During the study period, each episode of catheter-related infection was recorded.

Definition of Catheter-Related Infection

Cellulitis: erythema, induration, and tenderness around the area of the catheter reservoir or its tunnel.

Catheter-related sepsis: bacteremia documented during a febrile episode by at least one positive blood culture, central and/or peripheral.

Evaluation of Infectious Episodes

Details of all infectious complications were documented. Patients with ICVC who presented with fever were evaluated as follows: complete history and physical examination, complete blood cell count with differential, and urinalysis with culture and both peripheral and central blood cultures when possible. Blood cultures were placed into both aerobic and anaerobic culture bottles (BacT/Alert).

Staff Education

The pediatric house staff and nursing staff at the University of Miami/Jackson Memorial Medical Center were made aware of the study at the beginning of the study period and then intermittently during the study period. These "in-service sessions" included an audiovisual explanation of the appropriate technique in accessing these catheters, in addition to the explanation of the need to use only the assigned solution for the flushing of the catheters.

Bioavailability and Minimum Bactericidal Concentration (MBC) Testing

To determine the most appropriate antibiotic concentrations in the vancomycin/amikacin/heparin solution and the stability of the solution after 4 weeks in storage, the following investigations were performed. Clinical isolates of *Staphylococcus aureus* and *S. epidermidis*, *Pseudomonas aeruginosa*, and *Escherichia coli* were used. The isolates were obtained during a 2 month period from blood culture specimens submitted to Jackson Memorial Hospital's Microbiology Laboratory preceding the study. All specimens were subcultured from pure colonies in sheep's blood agar. Identification and antibiotics susceptibility testing of the organisms was performed using the Baxter Microscan™ Automated system. Both staphylococci were sensitive to vancomycin, and both gram negatives were sensitive to amikacin.

Six different antibiotic concentrations were prepared: 150 μg/ml, 100 μg/ml, 50 μg/ml, 25 μg/ml, and 12.5 μg/ml each of vancomycin and amikacin. A constant concentration of 100 units/ml of heparin was used. MBCs of the isolates were performed with each of the six antibiotic solutions twice: immediately after preparing the solutions and again 4 weeks later (after refrigerated storage at 20°C), as previously described [5,6]. The definition used for MBC was the highest dilution that will yield 99.9% killing.

TABLE II. Patient Characteristics in Relation to the Type of Flush Solution

	A	B	C	Total
No. of patients	33	28	3	64
No. of catheters	34	30	3	67
Median age/(range)[a]	114 (7–240)	109 (5–258)	87 (39–168)	107 (5–258)
Male/female	24/9	16/12	2/1	42/22
Total catheter days	10,033	9,814	853	20,700
Catheter days/patient[b]	295 ± 156	350 ± 173	170 ± 94	308 ± 165

[a]Months.
[b]Mean ± SD.
A: Standard solution (normal saline + heparin); B: study solution (normal saline + heparin + antibiotics); C: nonblinded study solution (normal saline + heparin + antibiotics).

RESULTS

Patient Characteristic

Sixty-nine patients were enrolled over a 17 month period from April 1992 to October 1993. All patients were monitored for catheter-related sepsis from the time of enrollment until the closing date of the study. Three patients were entered in an unrandomized fashion on solution C. Of the 66 patients randomized to receive either solution A or B, 61 were assessable. Five patients were not assessable for the following reasons: One adolescent refused to continue in the study, one patient was lost to follow-up, one patient had multiple catheter placements due to mechanical problems (i.e., catheter erosions and thromboses), one patient had his catheter flushed by nonstudy solution in another state, and finally one child had two surgical catheter-related sepses on two separate occasions, each time within a few days post catheter replacement, and on both occasions prior to the use of the appropriate study solution. All 64 patients (except two) were actively receiving chemotherapy during the study period. The diagnoses of the patients are detailed in Table I, and patient characteristics are summarized in Table II.

Biostability and MBC of Vancomycin/Amikacin/Heparin Solution

MBCs of the solution were achieved for antibiotic concentrations as low as 25 μg/ml for all studied organisms except for *E. coli*, for which the MBC was at a concentration of 50 μg/ml.

Catheter-Related Infections

During the study period, we documented five events of cellulitis and five events of catheter-related sepsis.Three events of catheter-related sepsis and three events of cellulitis occured in patients randomized to solution A (normal saline + heparin), whereas two events of catheter-related sepsis and two events of cellulitis occured in patients randomized to solution B (normal saline + heparin + antibiotics). The total rate of catheter-related infection was 0.49 infectious events/1,000 catheter days at risk. The rate of catheter-related sepsis was 0.24 sepsis/1,000 catheter days, and the rate of catheter-related bacterial sepsis was 0.14 sepses/1,000 catheter days. The etiology of sepsis in relation to study solution is detailed in Table III.

TABLE III. Etiology of Catheter-Related Sepsis in Relation to the Flush Solution

Patient no.	Solution	Organism
9	A	*Staphylococcus aureus*
13	A	*Candida tropicalis*
14	A	*Candida albicans*
26	B	*Staphylococcus epidermidis*
33	B	*Xanthomonas maltophilia*

A: Standard solution (normal + heparin); B: study solution (normal saline + heparin + antibiotics).

DISCUSSION

There are four potential sources for catheter colonization and catheter-related sepsis: the skin insertion site, the catheter hub, hematogenous seeding of the catheter, and infusate contamination [1]. The skin insertion site is the most important source. Although it is not clear how organisms enter the catheter, errors in sterile technique may play a role. It has been shown that certain strategies in catheter site care (i.e., topical antibiotics, avoiding the transparent plastic dressing) reduce the incidence of bacterial catheter-related infection [7,8]. Intervention to prevent bacteremia by interfering with luminal colonization of the ICVC plus good site care could decrease the incidence of catheter-related infection.

A number of researchers have tried to resolve whether flushing of the catheter with an antibiotic solutions is of value in preventing catheter-related sepsis. Ranson et al. [9] and Mckee et al. [10], in prospective, randomized trials, demonstrated that a single dose of vancomycin upon insertion of the catheter had no effect on the rate of catheter-related sepsis. MacKinnon et al. [11], in an unrandomized, unblinded study, found that prophylactic vancomycin increased the period the catheter remained in situ. In a prospective double-blind, randomized trial,

Schwartz et al. showed that the daily use of a vancomycin-containing flush solution for tunneled central venous catheters decreased the frequency of bacteremia with vancomycin-susceptible organisms [4]. For broader bacterial coverage and subsequent further improvement in catheter-related sepsis, the combination of vancomycin plus amikacin was used in our protocol.

All children in our study, with the exception of two, were being treated with chemotherapy for a variety of malignancies. To our knowledge, the rate of catheter-related sepsis reported herein is the lowest reported in the literature. We may speculate that the results obtained could be explained on the basis of the intensive staff education on the appropriate technique in handling ICVC. There is no controversy in the literature regarding the benefits of a motivated team adhering to a strict protocol can bring. Tomford et al. found that an intravenous therapy team reduced phlebitis from 32% to 15% [12]. The current trial confirms that strict sterile technique in handling ICVC would offer major protection against catheter-related sepsis.

In summary, with the current low rate of catheter-related sepsis, the efficacy of antibiotic prophylaxis could not be statistically evaluated. The question of prophylactic antibiotics loses significance when (1) ICVC-related infections can be kept at the current low rate simply through more thorough education regarding aseptic ICVC handling and (2) a significant percentage of fungal ICVC infection is not expected to be altered with prophylactic antibiotic use.

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